as unpalatable now as it ever was. At the very least it would seem reasonable to try to fine tune the use of the dollars that are available and to get the most out of them for truly needed, efficient and effective care for all.

MSMW

Antibiotic-Associated Colitis

THE COLON is a confusing and complicated anaerobic niche. It has been "guesstimated" that some 200 to 400 species of bacteria constitute half the organisms enumerated in this locale. The other half are yet to be named and the role of colonic anaerobes is still not well understood. These organisms are believed to be important in the degradation of many substances found in the succus entericus, such as enzymes, hormones and drugs, and in the metabolism of bile acids and vitamin K. By-products of this fermentative factory are primarily feces (composed of bacteria, water and undigested food) and flatus. It is no surprise then that antibiotics effect profound alterations in this milieu, which is the subject of the article presented in this month's journal by Stergachis and colleagues.

The incidence of antibiotic-associated colitis was analyzed from 1977 to 1980 for a large health care group located on Puget Sound. Approximately 280,000 patients were enrolled in the plan, and from previous studies it appeared that about 98% or more of all written prescriptions were fulfilled in this system. Thus it is likely that the authors had accurate data concerning the incidence of this disease associated with antibiotic therapy. In a group of 344 patients who were found to have colitis on discharge from their hospitals, antibiotic-associated colitis was diagnosed in four. It is unfortunate that the authors did not have the technology available to do either stool cultures or analyses for fecal toxins of *Clostridium difficile*. The clinical cases presented by the authors, however, do appear typical for clostridial enterocolitis.

In multiple studies *C difficile* has now been identified as the most common cause of antibiotic-associated colitis.[1] In several studies this organism has been found in from 3% to 6% of stool specimens (without toxin present) of normal humans. Apparently almost every antibiotic available on the market has induced this disease.[2] Therefore, colitis should be recognized as a complication of all antibiotics. This organism is also one of the first anaerobes to colonize the gastrointestinal tract of newborns, but does not produce any disease in this age group. The reasons for this paradox need further investigation.

The article also addresses what I believe is a realistic incidence of this disease (1.6 to 2.9 cases per 100,000 cases of patients exposed to antibiotics). These figures are primarily for oral therapy. When clindamycin was noted to be the major offender of this disease in 1977, clostridial colitis was misnamed "clindamycin colitis." At that time the manufacturer of clindamycin found an incidence of colitis of one case per 100,000 to 150,000 patient users. In-hospital patients receiving parenteral therapy may be more sensitive to colonization with *C difficile,* as this organism can be found in hospital environments,[3] and the infective dose for humans may be very small while they are taking antibiotics. In experimental hamsters, as few as one *C difficile* organism administered orally can precipitate fatal colitis if the animals are pretreated with an antibiotic to reduce colonization resistance within the gastrointestinal tract. It should also be recognized that this disease can be attributed to risk factors other than antibiotics, such as cytotoxic cancer chemotherapy, diabetes mellitus or hepatic failure.

The case histories presented in this month's journal also reiterate several clinical messages.[1,4] The first is that very trivial infections (such as toe infection, epididymitis, prostatitis and acne) treated with antibiotics can be associated with the occurrence of colitis. Second, the antibiotics were given orally and were commonly used ones such as dicloxacillin sodium, tetracycline and ampicillin. The symptoms of diarrhea can occur anywhere within a few days of initiating antibiotic therapy or up to six weeks after stopping antibiotics. In some patients, if the antibiotic therapy is continued, the diarrhea can be chronic, as was seen in one of their patients who continued to receive tetracycline and had five weeks of associated bloody diarrhea. While the authors found no cases attributable to the use of amoxicillin trihydrate, cephradine, erythromycin or penicillin, these antibiotics have been implicated with causation of colitis.[2] The authors also found no cases of colitis associated with the topical use of clindamycin in more than 1,500 cases. This is a popular regimen for acne that is believed effective. As the authors indicated, there have been a few cases of colitis seen with topical clindamycin because it is absorbed across the skin and can achieve levels within the colon sufficient to alter gastrointestinal flora.

Three of the four cases presented by Stergachis and co-workers were treated by stopping the precipitating antibiotics, and the fourth was treated with vancomycin. If a patient with colitis does not respond to elimination of the antibiotic, one can then administer orally and in divided doses (every 6 to 8 hours) either vancomycin (500 mg per day), metronidazole (1,000 mg a day) or bacitracin (100,000 units a day). Whereas the relapse rate following treatment with the first two agents is around 10% to 12%, almost all patients improve with a 5- to 7-day course of one of these three antibiotics.[5] Metronidazole has recently been shown by Teasley and associates to be as effective as vancomycin and is appealingly cheaper.[6]

In summary, their article addresses the incidence of a serious and sometimes morbid lesion in patients. The key point for all physicians is that all patients receiving antibiotics, particularly those who take them on a long-term basis, should be advised as to the complication of colitis. Also, patients should be queried by physicians if given long-term antibiotics for the presence of five or more loose stools a day, or stools that contain blood

or mucus. These are useful signs of possible colitis that should dictate other studies, or at least stopping the inducing antibiotic regimen.

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REFERENCES

1. Bartlett J: Antibiotic-associated pseudomembranous colitis. Rev Infect Dis 1979; 1:530-539
2. Silva J Jr, Fekety R: Clostridia and antimicrobial enterocolitis. Annu Rev Med 1981; 32:327-333
3. Fekety R, Kim KH, Brown D, et al: Epidemiology of antibiotic-associated colitis—Isolation of *Clostridium difficile* from the hospital environment. Am J Med 1981 Apr; 70:906-908
4. Mogg GAG, Keighley MRB, Burdon DW, et al: Antibiotic-associated colitis—A review of 66 cases. Br J Surg 1979; 66:738-742
5. Silva J, Batts DH, Fekety R, et al: Treatment of *Clostridium difficile* colitis and diarrhea with vancomycin. Am J Med 1981; 7:815-821
6. Teasley DG, Gerding DN, Olson M, et al: Prospective randomised trial of metronidazole versus vancomycin for *Clostridium difficile*-associated diarrhea and colitis. Lancet 1983; 2:1043-1046

How Much Toxicity Is Necessary?

SINCE THE FORMAL recognition of the specialty of medical oncology, and the provision of resources through the legislation of the National Cancer Act in 1971, considerable progress has been made in the management of neoplastic disease in the United States. Now almost 50% of patients with serious forms of cancer survive for five years, and many are regarded as cured. For patients younger than 45 years of age there has been a definite reduction in cancer mortality rates. To a large extent, this can be ascribed to the development of effective forms of cancer chemotherapy. The notable advances in the management of diseases such as acute lymphocytic leukemia, Hodgkin's disease and testicular cancer have, however, come at some cost, in particular in the form of clinical toxicity of the treatment used. In general, antineoplastic agents have a relatively low therapeutic index, exerting their cytotoxic action through a direct attack on either DNA or its synthesis. Their ability to discriminate efficiently between normal and target tissues is somewhat limited. As a consequence, a wide spectrum of adverse reactions is expected and has become generally accepted by the profession and the public as an unfortunate but necessary concomitant of treatment. The problem is further compounded by the fact that modern anticancer treatment rarely involves the use of a single cytotoxic agent; more commonly, cancer is treated with a combination of drugs—with overlapping toxicity for a single organ system—or with a combined modality approach in which anticancer drugs are given along with radiation therapy.

In this issue of the journal, McDonald and Tirumali present a comprehensive review of the many forms of toxic reaction of the gastrointestinal tract that are potentially associated with treatment with antineoplastic agents. This list of adverse reactions is impressive but must be placed in some context in regard to actual incidence. A serious or even clinically detectable hepatotoxic reaction, as an example, is unusual and rarely limits treatment. In addition, there is a considerable and largely unexplained variation in the degree of toxic effects experienced by patients treated with an identical regimen, with some patients having no effect while others are devastated. For the more subjective reactions, the frequency and magnitude of response may be influenced by a patient's preconceptions regarding chemotherapy, as well as the extent of preparation they have received and rapport they have established with the treating physician. Nevertheless, the more common toxic effects—anorexia, nausea and vomiting—can have serious consequences on the effectiveness of overall management. The reaction may be so severe as to limit a patient's acceptance of further, and possibly curative, treatment. Equally important, there can be a deleterious effect on patient nutrition, which compounds the all-too-frequent state of malnutrition that accompanies advanced cancer and the associated cachexia syndrome.

During the past seven years our understanding of the importance of toxic reactions of the gastrointestinal tract has become more focused and enlightened. This has resulted in the development of more effective antiemetic agents such as tetrahydrocannabinol and metoclopramide hydrochloride, as well as the establishment of nutritional supportive care as an essential component of overall management. In many cases a physician has a relatively broad range of chemotherapeutic options to select from; within limits, toxicity can be purposely reduced through the appropriate choice of drugs, dosage and schedule. This also assumes that a physician has accounted for the large number of additional variables that have been recognized to influence the risk of toxic effects, such as a patient's age, nutritional status and extent of prior therapy, and the clinical pharmacology of the drugs to be used. The medical and ethical difficulties encountered in patient selection and in determining a safe and effective dose for an individual case cannot be underestimated.

A critical question, and one fraught with considerable controversy, is what degree of toxic effects, if any, is required to insure that an optimal therapeutic dose has been administered. Under unusual circumstances, best exemplified by the current treatment of acute myelogenous leukemia, profound if not life-threatening hematologic and gastrointestinal toxic reactions are unavoidable. For most solid tumors, however, I strongly believe that serious adverse gastrointestinal reactions are not only unnecessary, but possibly avoidable. For example, many women who receive full-dose adjuvant chemotherapy following a mastectomy experience a stimulated appetite and have impressive weight gain during the 6 to 12 months of treatment. Studies using animals and clinical experience have shown that the current armamentarium of anticancer drugs has a definite but limited capability to select out and destroy cancer cells. This process is strongly influenced by complex mechanisms of neoplastic cell resistance and normal tissue tolerance. To simply increase drug dosage has rarely been shown to result in a measurable positive